apparatus involves both mass spectrometry and ion mobility spectrometry. That is, as described in much more detail in the Amendment dated June 26, 2003, the present invention provides for two-dimensional separation, in which the first separation step involves ion mobility spectrometry, and the second step involves mass spectrometry.

In addition to the usual advantages of two-dimensional separation, the combination of the present invention provides an additional advantage. That is, one of the disadvantages of time-of-flight mass spectrometers is that they inherently require pulsed intermittent operation. Once a pulse of ions has been injected into the flight tube of the mass spectrometer, it is necessary to wait until all of the ions in the sample have traveled the length of the flight tube and been detected before injecting the next pulse. Otherwise, late arriving ions from a previous pulse may contaminate a reading taken for a subsequent pulse. The need to wait until all of the ions have cleared the flight tube results in a poor duty cycle, particularly where the sample of ions has a wide m/z ratio.

One of the advantages of combining IMS with mass spectrometry is that there is an approximate correspondence between ion behavior and the two separation steps. Thus, in both IMS and low pressure mass spectrometry, a heavy ion will take longer to traverse the instrument due to a large m/z ratio. That is, a heavy ion will take longer to pass through a low pressure mass spectrometer, and will also have a low mobility resulting in a large drift or transit time through an IMS device. As a result, lighter ions will pass through the IMS device more quickly, while heavier ions take a longer time. This provides grouped input to the mass spectrometer, in which the faster ions are provided first and the m/z ratio range for each pulse or group is reduced as the IMS device has already separately grouped, to some extent, ions having widely different m/z ratios.

To some extent, ion output from the IMS must be modified before being accepted by the downstream low pressure mass spectrometer. That is, the diameter of the ion beam exiting the IMS section is much larger than the acceptance of the low pressure mass spectrometer as radial spread of the ion beam is inherent in the nature of IMS. Without modification, the resolution or sensitivity of a high performance, low pressure mass spectrometer would also be compromised.

Detailed Reply to Claim Rejections

Clemmer discloses a hybrid mobility-mass spectrometry apparatus involving both IMS and mass spectrometry. The diameter of the ion beam exiting the cell taught by Clemmer is much larger than the acceptance of the orthogonal time-of-flight analyzer. Clemmer attempts to narrow the ion beam by focusing the beam using ion optics in the form of a DC lens (Figure 4, reference No. 47).

As noted by the Examiner, Russ IV et al. discloses using a ring pole ion guide apparatus between mass spectrometer stages. The Examiner takes the position that Russ IV et al. discloses the suitability of using a ring pole ion guid apparatus between mass spectrometer stages to (1) focus the ions, and (2) provide a collision cell. The

Examiner then appears to take the further position that the teachings of Russ IV et al. regarding the suitability of the ring pole ion guide apparatus for these two purposes provides the necessary motivation to modify the Clemmer device by replacing the DC lens taught by Clemmer with the ring pole ion guide taught by Russ IV et al. For the reasons that follow, this position is respectfully traversed.

The Understandings in the Art Regarding RF Ion Guides

As set out in detail in the Amendment dated June 26, 2003, there is an understanding in the art that to use a RF ion guide as a focusing device will limit the resolution of the mobility spectrometer, as the RF ion guide will tend to "stretch" out the ion beam, thereby counteracting the tendency of the IMS device to provide a pulsed ion output. For your convenience, the relevant portions of the previously filed response dated June 26, 2003 are set out below.

This understanding in the art is illustrated in United States patent No. 6,331,702, as well as in two papers: A. N. Kructhinsky, I.V. Chemushevich, V.L. Spicer, W. Ens, and K. G. Standing, "Collisional Damping Interface for an Electrospray Ionization Time-of-Flight Mass Spectrometer", *Journal for the American Society of Mass Spectrometry*, 1998, Vol. 9, 569 to 579, published online by Elsevier Science; and, A. N. Kructhinsky, A.V. Loboda, V.L. Spicer, R. Dworschak, W. Ens, and K. G. Standing, "Orthogonal Injection of Matrix-assisted laser Desorption/Ionization ions into a Time-of-flight Spectrometer Through a Collisional Damping Interface"", *Rapid Communications in Mass Spectrometry*, 1998, Vol. 12, 508 to 518, published online by John Wiley & Sons. For example, column 7, line 21 to line 28 of United States patent No. 6,331,702 reads as follows:

> The RF quadrupoles 31 and 32 with a damping gas between their rods can be run in an RF-only mode, in which case they serve to reduce the axial energy, the radial energy, and the energy spreads, of the ions which pass through it, as will be described. This process substantially spreads the plume of ions out along the ion path, changing the initial beam, pulsed at about 13 Hz, into a quasi-continuous beam as described in more detail below.

The Collisional Damping paper describes an electrospray ionization (ESI) source, which is usually a continuous beam ion source, but has been adapted to pulse ions through an RF ion guide into a Time-of-flight mass spectrometer. Krutchinsky et al. investigate what happens to spatial integrity when these ions are pulsed into the ion guide. First, the authors describe a theoretical model that indicates that there is significant ion velocity damping when ions are transported through the ion guide. Specifically, on page 572, the authors describe damping by at least a factor of 6 for the radial velocity and by a factor of 14 for the axial velocity. These results are illustrated in Figs. 4a-d.

Secondly, the authors experimentally measure the time delay of ions passing through the RF ion guide. As reported on page 573, ions were pulsed every 300 microseconds

into the ion guide. As indicated in Fig. 6, these ions emerged from the exit of the ion guide spread over a width of 1.3 to 1.6 ms. That is, if ions are spatially separated by 300 microseconds upstream of the ion guide, they will tend to overlap leaving the ion guide. Any initial resolved mass distribution upstream of the ion guide will thus be lost downstream of the ion guide (as in the case where an ion mobility device was used to do the initial mass separation upstream from the RF ion guide).

The Orthogonal Injection paper describes using a MALDI ion source (a pulsed ion source) to inject ions through an RF ion guide to create a continuous beam of ions. The authors teach that by using the RF ion guide, the discrete pulses of ions are converted into a quasi-continuous beam as the collisional damping caused by the RF ion guide causes spreading of the ion beam out along the quadrupole axis (see page 513, last paragraph).

Based on the foregoing references, it is respectfully submitted that the use of an RF ion guide to focus an ion beam received from a mobility spectrometer would not have occurred to those skilled in the art as they would have concluded that the RF ion guide would counteract the tendency of the IMS to provide a pulsed ion output. There is nothing in the teachings of either Clemmer or Russ IV et al. to suggest replacing the DC lens taught by Clemmer with the RF or ring pole ion guide taught by Russ IV et al. Further, the shared understandings of those skilled in the art would militate against this combination. That this is the case can be inferred from the fact that neither Clemmer nor Russ IV et al. nor Thomson nor Smith teach the use of an RF ion guide for the purpose of focusing and maintaining the temporal spacing of ions between an ion mobility section and a mass analyzer section in a hybrid mobility-mass spectrometry apparatus despite the known problems with the Clemmer device resulting from its reliance on the DC lens.

Please note that this remains the case even given the suitability of the ring pole ion guide apparatus for other purposes. That is, the fact that Russ IV et al. teach that the ring pole ion guide is suitable to both focus the ions and to function as part of a collision cell, does not affect the understanding of those skilled in the art that an RF ion guide would tend to counteract the tendency of the IMS to provide a pulsed ion output, thereby reducing the efficacy of the hybrid mobility-mass spectrometry apparatus.

Based on the foregoing, it is respectfully submitted that claims 1, 16, 29 and 33 are unobvious over the teachings of the patents cited. That is, the subject matter covered by all of these claims involves an RF ion guide that generates a field to promote focusing of ions in the radial dimension along the axis of the RF ion guide. The use of an RF ion guide for this purpose is not taught in the prior art cited, nor is it consistent with the teachings of the prior art generally, which teachings indicate that an RF ion guide is unsuitable for this purpose as it will tend to spread out the pulses emitted by the IMS.

In view of the foregoing, it is respectfully submitted that claims are allowable over the cited references. Allowance of the application is respectfully requested.

If any questions arise, it is requested that the undersigned be contacted at the number provided below.

Respectfully submitted,

ALEXANDER V. LOBODA

Ian C. McMillan
Registration No. 43,390
/lbr
Encl.

Bereskin & Parr
Box 401
40 King Street West
Toronto, Ontario
Canada M5H 3Y2
Telephone: (416) 364-7311
Fax: (416) 361-1398